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### Authors

Waters, David D  
Hsue, Priscilla Y

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## PCSK9 Inhibition to Lower LDL-Cholesterol and Reduce Cardiovascular Risk Great Expectations

David D. Waters, Priscilla Y. Hsue

### Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events

Sabatine et al

*NEJM*. Online March 15, 2015. doi: 10.1056/NEJMoa1500858

### Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Robinson et al

*NEJM*. Online March 15, 2015. doi: 10.1056/NEJMoa1501031

**New clinical trials with the proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors evolocumab and alirocumab show that these drugs not only lower low-density lipoprotein cholesterol (LDL-C) profoundly, but also seem to reduce cardiovascular events, although the number of events and duration of follow-up are limited. Larger trials are underway to confirm these findings and to document safety.**

First identified as a causal gene for autosomal dominant hypercholesterolemia,<sup>1</sup> PCSK9 promotes the degradation of LDL-C receptors, resulting in higher blood levels LDL-C. Monoclonal antibodies to PCSK9, evolocumab, alirocumab, and bococizumab, all reduce LDL-C profoundly, and phase 3 clinical trials of these agents are hurtling toward completion.

Two recent reports of the effects of evolocumab and alirocumab have raised great expectations.<sup>2,3</sup> In the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) study,<sup>2</sup> 4465 patients who had completed one of several short-term studies were randomly assigned in a 2:1 ratio to receive either evolocumab 140 mg every 2 weeks or 420 mg monthly plus standard therapy or standard therapy alone. Median follow-up was 11.1 months. Evolocumab reduced LDL-C by 61% compared with standard therapy alone, from a median of 120 to 48 mg/dL, with the reduction remaining stable throughout follow-up. Cardiovascular events at 1 year were 2.18% in the standard therapy group and 0.95% in the

evolocumab group (hazard ratio 0.47; 95% confidence interval 0.28–0.78;  $P=0.003$ ).

In the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) study,<sup>3</sup> 2341 patients with heterozygous familial hypercholesterolemia or established coronary heart disease or a coronary heart disease risk equivalent, receiving maximally tolerated doses of statins, with an LDL-C  $\geq 70$  mg/dL, were randomly assigned in a 2:1 ratio to receive an alirocumab 150 mg or placebo subcutaneous injection every 2 weeks for 78 weeks. The primary efficacy end point, the percentage change in calculated LDL-C level from baseline to week 24, was reduced by 62% to a mean LDL-C of 48 mg/dL. In a post hoc analysis, the rate of major CV events was lower with alirocumab than with placebo (1.7% versus 3.3%; hazard ratio 0.52; 95% confidence interval 0.31–0.90;  $P=0.02$ ).

### Limitations

Several limitations of OSLER and ODYSSEY should be acknowledged. The follow-up in OSLER was slightly <1 year and only 60 patients had CV end point events.<sup>2</sup> Most of the events, 32, were coronary revascularizations; only 7 cardiovascular deaths, 14 myocardial infarctions, and 5 strokes occurred. It could be argued that coronary revascularization is a soft end point, particularly because follow-up was not blinded. Additionally, OSLER participants comprised a select population because they had already successfully completed an evolocumab study without adverse events.

Nearly twice as many CV events occurred in ODYSSEY as compared with OSLER, but the difference between treatment groups for these events was not statistically significant (4.6% versus 5.1%,  $P=0.68$ ).<sup>3</sup> In the post hoc analysis where only cardiovascular death, myocardial infarction, stroke, and unstable angina requiring hospitalization were counted, the event rates were much lower, 1.7% versus 3.3%, but this difference is statistically significant ( $P=0.02$ ).

In summary, the cardiovascular event results of OSLER and ODYSSEY are encouraging and point in the correct direction; however, they are analogous to early election results, with <5% of precincts reporting and only a small minority of the ballots counted.

### Efficacy

As shown by a meta-analysis of 14 trials involving 90056 participants, a 1 mmol/L (38.6 mg/dL) reduction in LDL-C with statins is associated with a 22% reduction in cardiovascular events (see Figure).<sup>4,5</sup> If this ratio were to hold true for PCSK9 inhibitors, one would expect cardiovascular events to

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Commentaries are edited by Aruni Bhatnagar & Ali J. Marian.

From the Division of Cardiology, San Francisco General Hospital, and the Department of Medicine, University of California, San Francisco.

Correspondence to David D. Waters, MD, Division of Cardiology, Room 5G1, San Francisco General Hospital, 1001 Potrero Ave, San Francisco, CA 94114. E-mail David.Waters@ucsf.edu

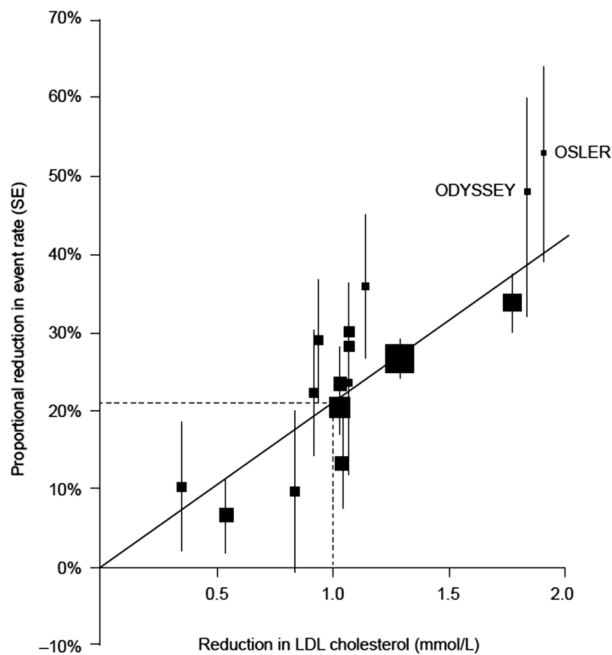
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**Figure. Relationship between reduction in low-density lipoprotein cholesterol (LDL-C) in mmol/L (x axis) and percentage reduction in vascular events (y axis) in 14 clinical trials with statins.** The results of OSLER and ODYSSEY have been added (top right), showing that the potential benefit of PCSK9 inhibitors is larger than that of statins. ODYSSEY indicates Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy; and OSLER, Open-Label Study of Long-Term Evaluation against LDL Cholesterol. Adapted from Baigent et al<sup>5</sup> with permission of the publisher (Elsevier, 2005).

be reduced by nearly half. Statins possess anti-inflammatory effects that may contribute to event reduction, particularly in acute coronary syndromes, where levels of inflammatory markers are high. At the time of this writing, no published data indicates that PCSK9 inhibitors reduce inflammatory markers, such as high-sensitivity C-reactive protein. However, PCSK9 inhibitors do reduce lipoprotein (a) by 25% to 30%.<sup>2,3,6</sup> High lipoprotein (a) levels are a well-defined marker of cardiovascular risk and are not reduced by statins.

The relative risk reduction with statins is independent of baseline LDL-C level.<sup>4,5</sup> Statin-treated patients in clinical trials who achieved on-treatment LDL-C levels of <50 mg/dL had lower cardiovascular event rates compared with higher on-treatment LDL-C strata,<sup>7</sup> but this observation might be confounded by other favorable factors, such as better compliance. More patients achieve extremely low LDL-C levels with PCSK9 inhibition compared with statins; for example, in ODYSSEY, 37.1% of alirocumab-treated participants had 2 consecutive measurements of LDL-C <25 mg/dL,<sup>3</sup> and in OSLER, the minimum LDL-C attained was <25 mg/dL in 26% of evolocumab-treated patients.<sup>2</sup> Whether further event reduction occurs at these extreme levels is unknown.

The foregoing considerations add some uncertainty to any prediction about the degree of benefit of PCSK9 inhibitors. However, treatments without serious adverse consequences that reduce LDL-C have consistently been shown to reduce cardiovascular events in clinical trials: ezetimibe,

cholestyramine, even ileal bypass surgery. In other words, LDL-C has functioned well as a surrogate marker.

## Safety

Several CV drugs that initially appeared promising (cerivastatin, torcetrapib, rimonabant, laropiprant) ultimately failed because of off-target toxicity. Could such a fate befall PCSK9 inhibitors?

The rates of serious adverse events in both OSLER and ODYSSEY were similar in the active treatment and comparator groups.<sup>2,3</sup> Injection site reactions occurred in 5.9% of alirocumab-treated patients and 4.2% of placebo-treated patients in ODYSSEY ( $p=NS$ ) and in 4.3% of evolocumab-treated patients in OSLER. The comparator group in OSLER did not receive placebo, and the open-label follow-up may have influenced adverse event reporting. Muscle-related adverse events were not significantly more common with evolocumab plus standard therapy compared with standard therapy alone, but in ODYSSEY, myalgia was reported in 5.4% of alirocumab-treated patients and 2.9% of placebo patients ( $P=0.006$ ). Creatine kinase and hepatic enzymes levels were not elevated in PCSK9 inhibitor-treated patients in either trial.

The adverse event that has drawn the most scrutiny in PCSK9 inhibitor studies is neurocognitive defects. This term covers an array of symptoms, including amnesia, memory impairment, delirium, confusion, and other related conditions. In OSLER, neurocognitive defects were reported in 0.9% of evolocumab-treated and 0.3% of control patients (relative risk 3.37, 95% confidence interval 1.18–9.63,  $P=0.023$ ). In ODYSSEY, these events were seen in 1.2% of alirocumab-treated patients and in 0.5% of placebo-treated patients (relative risk 2.29, 95% confidence interval 0.78–6.74,  $p=NS$ ). Neurocognitive defects did not correlate with low on-treatment LDL-C levels in either trial, although the data are too sparse to be certain that such a relationship does not exist.

In February 2012, the US Food and Drug Administration in a safety update on statins added to the label the warning that generally nonserious and reversible cognitive side effects (memory loss, confusion, etc.) had been reported with statins.<sup>8</sup> Such neurocognitive side effects had not been noted in statin trials or meta-analyses<sup>4,5</sup> and a recent systematic review concluded that the published data do not suggest an adverse effect of statins on cognition.<sup>9</sup> Nevertheless, it is tempting to jump to the conclusion that low LDL-C levels caused by statins or PCSK9 inhibitors interfere with cognition.

Evidence against this conclusion comes from the rare genetic defect, abetalipoproteinemia, where LDL-C levels are undetectable from birth.<sup>10</sup> Affected individuals have a variety of serious problems, mainly as a result of fat and fat-soluble vitamin malabsorption, but they have not been reported to have neurocognitive defects. Additionally, a young African woman, homozygous for the PCSK9 nonsense mutation C679X, has been reported with total absence of PCSK9 and an LDL-C level of 0.4 mmol/L (15 mg/dL).<sup>11</sup> She is completely healthy.

## Great Expectations

This commentary focuses on PCSK9 inhibitors, but the drug development pipeline is full of potentially beneficial drugs that affect lipid metabolism, through a variety of different

mechanisms.<sup>12</sup> The cholesteryl ester transfer protein inhibitors anacetrapib and evacetrapib are furthest along, in large definitive phase 3 trials, ahead of the PCSK9 inhibitors. The PCSK9 genetic defects have provided encouragement for the development of PCSK9 inhibitors. From the report of the genetic mutation in 2003<sup>1</sup> to understanding the structure and function of PCSK9 to developing and testing anti-PCSK9 antibodies in clinical trials has taken a remarkably short period of time.

Charles Dickens' novel *Great Expectations* was popular when it was first published in serial form beginning in 1860. However, the ending was criticized as being too sad, so Dickens rewrote it to suggest that the protagonists Pip and Estella might have a future together. With respect to the future of PCSK9 inhibitors, a quote from the novel might temper our great expectations: "Take nothing on its looks; take everything on evidence. There's no better rule."<sup>13</sup>

### Disclosures

Dr Waters has received honoraria from Sanofi-Aventis, Pfizer, and Regeneron for participating in clinical trial committees. Dr Hsue has received honoraria from Amgen.

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